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(71) Applicant: SCIMED LIFE SYSTEMS, INC. [US/US]; One SciMed Place, Maple Grove, MN 55311-1566 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BUISER, Marcia [US/US]; 480 Belmont Street, Apt. #2, Watertown, MA 02472 (US). BELLISARIO, Marc [US/US]; 1 Florence Street, Cambridge, MA 02139 (US). KNAPP, David [US/US]; 1352 Goodrich Avenue, Saint Paul, MN 55105 (US). MANGIN, Stephan [US/US]; 381 Eliot Street, Apt. #3, Ashland, MA 01721 (US). LANPHERE, Janel [US/US]; 76 Cloverdale Road, Newton, MA 02461 (US).

(74) Agent: GAGEL, John, J.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

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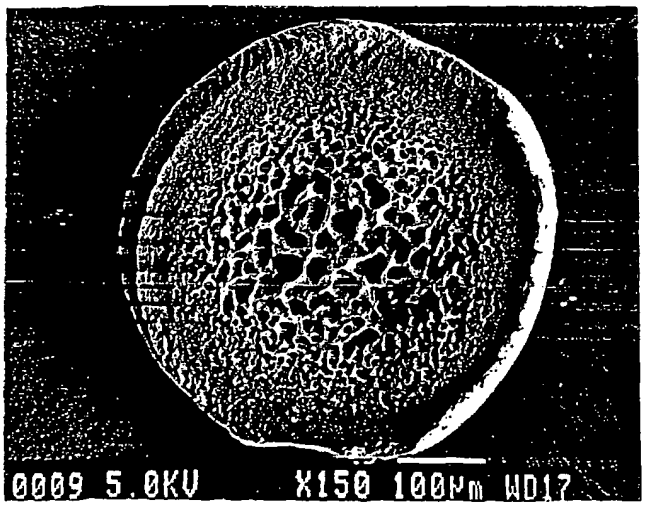

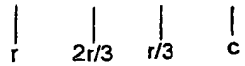

(57) Abstract: Embolic polymer particles are described. For example, the particles include pores such that the predominant size of pores near the center of particles is greater than the predominant size of pores adjacent to periphery of the particle.

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EMBOLIZATION

TECHNICAL FIELD

This invention relates to embolization.

BACKGROUND

Therapeutic vascular occlusions (embolizations) are used to prevent or treat pathological conditions *in situ*. Compositions including embolic particles are used for occluding vessels in a variety of medical applications. Delivery of embolic particles through a catheter is dependent on size uniformity, density and compressibility of the embolic particles.

SUMMARY

In a first aspect, the invention features an embolic composition. The composition includes substantially spherical embolic particles having a diameter of about 1200 micron or less. The particles include polyvinyl alcohol and an interior having relatively large pores and a surface region with fewer relatively large pores.

In another aspect, the invention features an embolic composition including embolic polymer particles having a diameter of about 1200 micron or less and a surface with a predominant pore size of about 2 micron or less and pores interior to surface of about 10 micron or more.

In another aspect, the invention features an embolic composition including embolic polymer particles including a surface region from about 0.8r to r, the predominant pore size in the surface region being smaller than the predominant pore size in a region C to 0.3r.

In another aspect, the invention features an embolic composition, including embolic particles with a surface region defined primarily by relatively small pores and an interior region defined primarily of relatively large pores.

In another aspect, the invention features a method of manufacturing embolic particles. The method includes generating drops of a base polymer and a gelling compound and combining the particles with a pharmaceutically acceptable medium. The method may optionally include reacting the base polymer and removing the gelling

compound. In another aspect, the invention features forming embolic particles by nebulization such as vibratory nebulization.

In another aspect, the invention features embolic compositions including particles formed by the processes described herein.

In another aspect, the invention features a method of delivering a therapeutic agent to a patient. The method includes administering to a patient in need of an embolization a therapeutically effective amount of substantially spherical embolic polymer particles. The particles include polyvinyl alcohol and include an interior region having relatively large pores and a surface region having fewer relatively large pores.

Embodiments may also include one or more of the following. The relatively large pores are about 20 or 30 micron or more. The surface region is about r to 0.8r. The surface region is about r to 2/3r. The particles include a body region from about 2/3r to $^{r}/_{3}$ including intermediate size pores and the body region has more intermediate size pores than the surface region. The center region is from about $^{r}/_{3}$ to C, the outer region including large size pores and the body region has fewer large size pores than the center region. The intermediate size pores are about 2 to 18 microns. The surface region is substantially free of pores greater than about 5 micron.

Embodiments may also include one of the following. The predominant pore size progressively increases from surface to the center of the particle. The predominant pore size on the particle surface is about 1 micron or less. The particles have a surface region from about (2r)/3 to the surface wherein the predominant pore size is in the range of about 1 micron or less. The predominant pore size is about 0.1 micron or less. Interior of said surface region, the particles have a predominant pore size in the range of about 2 to 35 microns. The particles include a center region from about r to r/3 in which the predominant pore size is about 20 to 35 micron. The particles have a body region from r/3 to (2r)/3 in which the predominant pore size is about 2 to 18 micron. The particles have a surface region from about (2r)/3 to the periphery and the predominant pore size in the surface region is about 10% or less than the predominant pore size in the interior to the surface region. The particles include a surface region from about 0.8r to r wherein the predominate pore size is about 1 micron or less. The particles include a region from about C to 0.8r includes pores having a diameter of 10 microns or more. The region C to 0.8r has a predominant pore size of about 3.5 to 2

micron. The particles have a density of about 1.1 to about 1.4 g/cm3. The particles have a density of about 1.2 to 1.3 g/cm3. The embolic particles have a sphericity of about 90% or more. The particles have an initial sphericity of about 97% or more. The particles have a sphericity of about 0.90 after compression to about 50%. The particles have a size uniformity of about + 15% or more.

Embodiments may also include one or more of the following. The particles include about 1% or less polysaccharide. The polysaccharide is alginate. The alginate has a guluronic acid content of about 60% or greater. The embolic particles are substantially insoluble in DMSO. The embolic particles are substantially free of animal-derived compounds. The polyvinyl alcohol is composed of substantially unmodified polyvinyl alcohol prepolymer. The polyvinyl alcohol is predominantly intrachain 1, 3-diols acetalized. The composition includes saline and/or contrast agent. The particles and/or composition are sterilized.

Embodiments may also include one or more of the following. The gelling compound is a polysaccharide The gelling compound is alginate. The alginate has a guluronic acid content of about 60% or more. The drops are contacted with a gelling agent. The gelling agent is a divalent cation. The cation is Ca+2. The base polymer is PVA. The PVA is reacted by acetalization. The PVA has a molecular weight of about 75,000 g/mole or greater. The viscosity of the base polymer and gelling compound is modified prior to forming said drops. The viscosity is modified by heating. The drops are formed by vibratory nebulization.

Embodiments may also include one or more of the following. Administration is by percutaneous injection. Administration is by a catheter. The particles are introduced to the body through a lumen, and the lumen has a smaller diameter than the particles. The composition is used for treatment of uterine fibroids. The composition is used for treatment of tumors, including hypervascular tumors and for arteriovenous malformations (AVMs).

Embodiments of the invention may have one or more of the following advantages. Some disorders or physiological conditions can be mediated by delivery of embolic compositions. Embolic compositions can be used, for example, in treatment of fibroids, internal bleeding AVMs and hypervascular tumors. Fibroids can include uterine fibroids which grow within the uterine wall, on the outside of the uterus, inside the uterine cavity, between the layers of broad ligament supporting the uterus, attached

to another organ or on a mushroom-like stalk. Internal bleeding includes gastrointestinal, urinary, renal and varicose bleeding. AVMs are, for example, abnormal collections of blood vessels which shunt blood from a high pressure artery to a low pressure vein, resulting in hypoxia and malnutrition of those regions from which the blood is diverted.

Spherical embolic particles in the embolic compositions can be tailored to a particular application by varying particle size, porosity gradient, compressibility, sphericity and density of the particles. The uniform size of the spherical embolic particles can, for example, fit through the aperture of a catheter for administration by injection to a target site without partially or completely plugging the lumen of the catheter. The spherical embolic particles have a diameter of about 1200 micron or less. Size uniformity of $\pm$ 15% of the spherical embolic particles allows the particles to stack evenly in the cylindrical lumen of the blood vessel to completely occlude the blood vessel lumen. Suspensions containing the embolic particles at density of about 1.1 to about 1.4 g/cm^3 can be prepared in calibrated concentrations of the embolic particles for ease of delivery by the physician without rapid settlement of the suspension. Control in sphericity and uniformity of the embolic particles can result in reduction in aggregation caused, for example, by surface interaction of the particles. In addition, the embolic particles are relatively inert in nature.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1A is a schematic illustrating injection of an embolic composition including embolic particles into a vessel, while **FIG. 1B** is a greatly enlarged view of the region A in **FIG. 1A**;

FIG. 2A is a light micrograph of a collection of hydrated embolic particles, while **FIG. 2B** is a scanning electron microscope (SEM) photograph of the embolic particle surface and **FIGS. 2C-2E** are cross-sections of embolic particles;

FIG. 3A is a schematic of the manufacture of an embolic composition while **FIG. 3B** is an enlarged schematic of region A in **FIG. 3A**;

FIG. 4 is a photograph of gel-stabilized drops;

FIG. 5 is a graph of embolic particle size uniformity; and

FIG. 6 is a schematic of an injection pressure testing equipment;

FIG. 7 is an infrared spectrum of embolic particles.

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

Composition

Referring to **FIGS. 1A** and **1B**, an embolic composition **100**, including embolic particles **111** and carrier fluid, is injected into a vessel through an instrument such as a catheter **150**. The catheter is connected to a syringe barrel **110** with a plunger **160**. The catheter **150** is inserted, for example, at the leg of a patient into a femoral artery **120** to deliver the embolic composition **100** to, for example, occlude a uterine artery **130** leading to a fibroid **140**. The fibroid **140** is located in the uterus of a female patient. The embolic composition **100** is initially loaded into the syringe **110**. The plunger **160** of syringe **110** is compressed to deliver the embolic composition **100** through the catheter into lumen of the uterine artery **130**.

Referring particularly to **FIG. 1B** which is an enlarged view of section A of **FIG. 1A**, the uterine artery **130** is subdivided into smaller uterine vessels **170** (about 2 mm or less) which feed a uterine fibroid **180**. The embolic particles **111** in embolic composition **100** partially or totally fill the lumen of uterine artery **130**, either partially or completely occluding the lumen of the uterine artery **130** feeding the uterine fibroid **140**.

The particles are substantially formed of polymer such as a highly water insoluble, high molecular weight polymer. As will be discussed below, a preferred polymer is high molecular weight polyvinyl alcohol (PVA) that has been acetalized. Preferably, the embolic particles are substantially pure intrachain 1,3 acetalized PVA and substantially free of animal derived residue such as collagen. In embodiments, the particles include a minor amount, e.g. less than about 0.2 weight %, of alginate or another polysaccharide or gelling material.

Referring to **FIG. 2A**, embolic particles **111** have a substantially uniform spherical shape and size. Referring to **FIG. 2B**, each embolic particle has a well-defined outer spherical surface including relatively small, randomly located pores. The

surface appears substantially smooth, with some larger surface morphology such as crevice-like features. Referring to FIGS. 2C-2E, SEM images of cross-sections through embolic particles, the body of the particle defines pores which provide compressibility and other properties to the embolic composition. Pores near the center of the particle are relatively large and pores near the surface of the particle are relatively small.

The region of small pores near the periphery of the embolic particle is relatively stiff and incompressible, which enhances resistance to shear forces and abrasion. In addition, the variable pore size profile produces a symmetric compressibility and, it is believed, a compressibility profile such that the particles are relatively easily compressed from a maximum, at rest diameter to a smaller, compressed first diameter but compression to even smaller diameter requires substantially greater force. A variable compressibility profile is believed to be due to the presence of a relative weak, collapsible inter-pore wall structure in the center region where the pores are large, and a stiffer inter-pore wall structure near the surface of the particle, where the pores are more numerous and relatively small. The variable pore size profile also is believed to enhance elastic recovery after compression. The pore structure also influences the density of the embolic particles and the rate of carrier fluid or body fluid uptake.

The embolic particles can be delivered through a catheter having a lumen area that is smaller, e.g. 50% smaller or less, than the uncompressed cross-sectional area of the particles. As a result, the embolic particles must be compressed to pass through the catheter for delivery into the body. The compression force is provided indirectly by increasing the pressure applied to the carrier fluid by depressing the syringe plunger. The embolic particles are relatively easily compressed to diameters sufficient for delivery through the catheter into the body. The robust, rigid surface region resists abrasion when the embolic particles contact hard surfaces such as syringe surfaces, hard plastic or metal stopcock surfaces, and the catheter lumen wall (e.g. Teflon) during delivery. Once in the body, the embolic particles substantially recover to original diameter and shape for efficient transport in the carrier and body fluid stream. At the point of occlusion, the particles can again compress as they aggregate in the occlusion region. The embolic particles form a dense occluding mass. The compression in the body is determined by the force provided by body fluid flow in the lumen. The

compression may be limited by the compression profile of the particles and the number of embolic particles needed to occlude a given diameter may be reduced.

In embodiments, the particles have a diameter of about 1500 or 1200 microns or less, and about 10 microns or more, e.g. about 400 microns or more and the pores are about 50 or 35 to 0.01 micron. The embolic particles can be classified in size ranges of about 500-700 microns, about 700-900 microns, or about 900-1200 microns. The particles typically have a mean diameter in approximately the middle of the range and variance of about 20% or less, e.g. 15% or 10% or less.

Referring particularly to **FIG. 2C**, the particles can be considered to include a center region, C, from the center of the particle to a radius of about r/3, a body region, B, from about r/3 to about 2 r/3 and a surface region, S, from 2r/3 to r. The regions can be characterized by the relative size of the pores and the number of pores of given sizes. In embodiments, the center region has a greater number of relatively large pores than the body region and the surface region. The large pores are in the range of about 20 micron or more, e.g. 30 micron or more, or in the range of about 20 to 35 micron. The body region has a greater number of intermediate size pores than the surface region. The intermediate size pores are in the range of about 5 to 18 micron. In embodiments, the regions may also have different densities, with the density of the surface region being greater than the density of the body region, and the density of the body region being greater than the density of the center region.

The size of the pores in each of the regions can also be characterized by a distribution. In embodiments, the predominant pore size(s) in the center region being greater than the predominant pore size(s) in the body region and the predominant pore size(s) in the body region is greater than the predominant pore size(s) in the surface region. In embodiments, in the predominant pore size in the center region is 20 micron or more, e.g. 30 microns or more, or in the range of about 20 to 35 microns. The predominant pore size in the body region is about 18 micron or less, e.g. about 15 micron or less, or in the range of about 18 to 2 micron. The pores in the surface region are preferably predominantly less than about 1 micron, e.g. about 0.1 to 0.01 micron.

In embodiments, the predominant pore size in the body region is about 50 to 70% of the pore size in the center region and the pore size in the surface region is about 10% or less, e.g. about 2% of the pore size in the body region. The size of the pores on the outer surface of the particle is predominantly in the range of about 1 micron or less,

e.g. about 0.1 or 0.01 micron. In embodiments, the surface and/or surface region is substantially free of pores having a diameter larger than about 10 micron or larger than about 1 micron. In embodiments, the predominant pore size is in the region 0.8 or 0.9r to r is about 1 micron or less, e.g. 0.5 to 0.1 micron or less. The region from the center of the particle to 0.8 or 0.9r has pores of about 10 micron or greater and/or has a predominant pore size of about 2 to 35 micron. In embodiments, the predominant pore size in the region 0.8 or 0.9r to r is about 5% or less, e.g. 1% or 0.3% or less than the predominant pore size in the region from the center to 0.9r. the largest pores in the particles can have a size in the range of 1% or 5% or 10% or more of the particle diameter.

The size of the pores can be measured by viewing a cross-section as in Fig. 2C. For irregularly shaped pores, the maximum visible cross-section is used. The predominant pore size(s) can be found by measuring the size of the visible pores and plotting the number of pores as a function of size. The predominant pore size(s) are the sizes that are about the maximum in the distribution. In Fig. 2C, the SEM was taken on wet particles including absorbed saline, which were frozen in liquid nitrogen and sectioned. (Fig. 2B was taken prior to sectioning.) In Figs. 2D and 2E, the particle was freeze-dried prior to sectioning and SEM analysis.

The density of the particles is such that they are readily suspended in the carrier fluid such as a mixture of saline and contrast solution and remain suspended during delivery. In embodiments, the density is in about 1.1 - 1.4g/cm^3. For suspension in a saline-contrast solution, the density is about 1.2 - 1.3g/cm^3. The sphericity after compression in a catheter to about 50% or more of their cross-sectional area is about 0.90 or 0.95 or greater. In embodiments, the particles can be manually compressed, essentially flattened, while wet to less than 50% of original diameter and then, upon exposure to fluid, regain a sphericity of about 0.9 or more. The carrier fluid is a pharmaceutically acceptable carrier such as saline or contrast agent. The particles can be sterilized prior to use.

Manufacture

Referring to **FIG. 3A**, a system for producing embolic particles includes a flow controller **300**, a drop generator **310**, a gelling vessel **320**, a reactor vessel **330**, a gel dissolution chamber **340** and a filter **350**. The flow controller **300** delivers polymer

solutions to a viscosity controller **305**, which heats the solution to reduce viscosity prior to delivery to the drop generator **310**. The drop generator **310** forms and directs drops into a gelling vessel **320**, where drops are stabilized by gel formation. The gel-stabilized drops are transferred from the gelling vessel **320** to reactor vessel **330** where the polymer in the gel-stabilized drops are reacted forming precursor particles. The precursor particles are transferred to a gel dissolution chamber **340**, where the gel is dissolved. The particles are then filtered in a filter **350** to remove debris, sterilized, and packaged as an embolic composition including embolic particles.

A base polymer and a gelling precursor are dissolved in water and mixed. The mixture is introduced to a high pressure pumping apparatus, such as a syringe pump (e.g., model PHD4400, Harvard Apparatus, Holliston, MA). Examples of base polymers include polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, poly vinyl sulfonate, carboxymethyl cellulose, hydroxyethyl cellulose, substituted cellulose, polyacrylamide, polyethylene glycol, polyamides, polyureas, polyurethanes, polyester, polyethers, polystyrene, polysaccharide, polylactic acid, polyethylene, polymethylmethacrylate and copolymers or mixtures thereof. A preferred polymer is polyvinyl alcohol. The polyvinyl alcohol, in particular, is hydrolyzed in the range of 80 to 99%. The weight average molecular weight of the base polymer can be in the range of 9000 to 186,000, 85,000 to 146,000 or 89,000 to 98,000. Gelling precursors include, for example, alginates, alginate salts, xanthan gums, natural gum, agar, agarose, chitosan, carrageenan, fucoidan, furcellaran, laminaran, hypnea, eucheuma, gum arabic, gum ghatti, gum karaya, gum tragacanth, hyalauronic acid, locust beam gum, arabinogalactan, pectin, amylopectin, other water soluble polysaccharides and other ionically crosslinkable polymers. A particular gelling precursor is sodium alginate. A preferred sodium alginate is high guluronic acid, stem-derived alginate (e.g. about 50 or 60% or more guluronic acid with a low viscosity e.g. about 20 to 80 cps at 20°C) which produces a high tensile, robust gel. High molecular weight PVA is dissolved in water by heating, typically above about 70°C, while alginates can be dissolved at room temperature. The PVA can be dissolved by mixing PVA and alginate together in a vessel which is heated to autoclave temperature (about 121°C). Alternatively, the PVA can be disposed in water and heated and the alginate subsequently added at room temperature to avoid exposing the alginate to high temperature. Heat can also be applied by microwave application. In embodiments, for PVA/alginate, the mixture is

typically about 7.5 to 8.5%, e.g. about 8% by weight PVA and about 1.5 to 2.5%, e.g. about 2%, by weight alginate.

Referring to **FIG. 3B**, the viscosity controller **305** is a heat exchanger circulating water at a predetermined temperature about the flow tubing between the pump and drop generator. The mixture of base polymer and gelling precursor flows into the viscosity controller **305**, where the mixture is heated so that its viscosity is lowered to a level for efficient formation of very small drops. For a high molecular weight PVA/alginate solution, the temperature of the circulating water is less than about 75°C and more than about 60°C, for example, 65°C which maintains the mixture at a viscosity of 90-200 centipoise. For spherical particles, the viscosity of the drops is maintained so they are captured in the gelling vessel without splintering or cojoining which can create irregular, fiberous particles. In other embodiments, the flow controller and/or the drop generator can be placed in a temperature-controlled chamber, e.g. an oven, or a heat tape wrap, to maintain a desired viscosity.

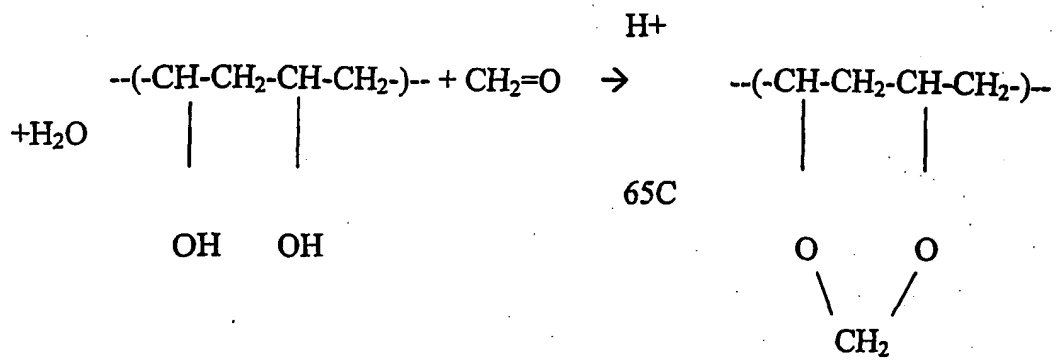
The drop generator **310** generates substantially spherical drops of predetermined diameter by forcing a stream of the mixture of base polymer and gelling precursor through a nozzle which is subject to a periodic disturbance to break up the jet stream into drops. The jet stream can be broken into drops by vibratory action generated for example, by an electrostatic or piezoelectric element. The drop size is controlled by controlling the flow rate, viscosity, amplitude, and frequency at which the element is driven. Lower flow rates and higher frequencies produce smaller drops. A suitable electrostatic drop generator is available from NISCO Engineering, model NISCO Encapsulation unit VAR D, Zurich, Switzerland. In embodiments, the frequency is in the range of about 0.1 to 0.8 kHz. The flow rate through the droplet generator is in the range of about 1 to 12 mL per minute. The drop generator can include charging the drops after formation such that mutual repulsion between drops prevents drop aggregation as drops travel from the generator to the gelling vessels. Charging may be achieved by, e.g. an electrostatic charging device such as a charged ring positioned downstream of the nozzle.

Drops of the base polymer and gelling precursor mixture are captured in the gelling vessel **320**. The gelling vessel **320** contains a gelling agent which interacts with the gelling precursor to stabilize drops by forming a stable gel. Suitable gelling agents include, for example, a divalent cation such as alkali metal salt, alkaline earth metal salt

or a transition metal salt that can ionically crosslink with the gelling agent. An inorganic salt, for example, a calcium, barium, zinc or magnesium salt can be used as a gelling agent. In embodiments, particularly those using an alginate gelling precursor, a suitable gelling agent is calcium chloride. The calcium cations have an affinity for carboxylic groups in the gelling precursor. The cations complex with carboxylic groups in the gelling precursor resulting in encapsulation of the base polymer in a matrix of gelling precursor.

Referring to **FIG. 4**, a photo-image of the gelled particles, the gelling agent is in an amount selected in accordance with the desired properties of the particles. As evident, a pore structure in the particle forms in the gelling stage. The concentration of the gelling agent can control pore formation in the particle, thereby controlling the porosity gradient in the embolic particle. Adding non-gelling ions, for example, sodium ions, to the gelling solution can reduce the porosity gradient, resulting in a more uniform intermediate porosity throughout the particle. In embodiments, the gelling agent is, for example, 0.01-10 weight percent, 1-5 weight percent or 2 weight percent in deionized water. In embodiments, particles, including gelling agent and a pore structure can be used in embolic compositions.

Following drop stabilization, the gelling solution is decanted from the solid drops and the stabilized drops are transferred to the reactor vessel **330**. In the reactor vessel **330**, the stabilized drops are reacted to produce precursor particles. The reactor vessel includes an agent that chemically reacts with the base polymer, e.g. to cause crosslinking between polymer chains and/or within a polymer chain. The agent diffuses into the stabilized drops from the surface of the particle in a gradient which, it is believed, provides more crosslinking near the surface of the stabilized drop compared to the body and center of the drop. Reaction is greatest at the surface of the drop, providing a stiff, abrasion resistant exterior. For polyvinyl alcohol, for example, the vessel **330** includes aldehydes, such as formaldehyde, glyoxal, benzaldehyde, aterephthalaldehyde, succinaldehyde and glutaraldehyde for the acetalization of polyvinyl alcohol. The vessel **330** also includes an acid, for example, strong acids such as sulfuric acid, hydrochloric acid, nitric acid and weak acids such as acetic acid, formic acid and phosphoric acid. In embodiments, the reaction is primarily a 1,3 acetalization:



This intra-chain acetalization reaction can be carried out with relatively low probability of inter-chain crosslinking as described in John G. Pritchard "Poly(Vinyl Alcohol) Basic Properties And Uses (Polymer Monograph, vol. 4) (see p. 93-97), Gordon and Breach, Science Publishers LTD., London, 1970, the entire contents of which is hereby incorporated by reference. Some OH groups along a polymer chain may remain unconverted since the reaction proceeds in a random fashion and there will be left over OH groups that do not react with adjacent groups.

Adjusting the amount of aldehyde and acid used, reaction time and reaction temperature can control the degree of acetalization. In embodiments, the reaction time is e.g., 5 minutes to 1 hour, 10 to 40 minutes or 20 minutes. The reaction temperature can be 25°C to 150°C or 75°C to 130°C or 65°C. The reactor vessel is placed in a water bath fitted with a orbital motion mixer. The crosslinked precursor particles are washed several times with deionized water to neutralize the particles and remove any residual acidic solution.

The precursor particles are transferred to the dissolution chamber **340** to remove the gelling precursor, e.g. by an ion exchange reaction. In embodiments, sodium alginate is removed by ion exchange with a solution of sodium hexa-metaphosphate (EM Science). The solution can include, for example, ethylenediaminetetracetic acid (EDTA), citric acid, other acids and phosphates. The concentration of the sodium hexa-metaphosphate can be, for example, 1-20 weight %, 1-10 weight % or 5 weight % in deionized water. Residual gelling precursor, for example, sodium alginate, can be determined by assay for detection of uronic acids in, for example, alginates containing mannuronic and guluronic acid residues. Suitable assays include rinsing the particles with sodium tetraborate in sulfuric acid solution to extract alginate and combining the extract with metahydroxydiphenyl colormetric reagent and determining concentration by UV/VIS spectroscopy. Testing can be carried out by alginate suppliers such as

FMC Biopolymer, Oslo, Norway. Residual alginate may be present in the range of about 20-35% by weight prior to rinsing and in the range of about 0.01-0.5% or 0.1-0.3% or 0.18% in the particles after rinsing for 30 minutes in water at about 23°C.

The particles are filtered through filter 350 to remove residual debris. Particles of 500 to 700 microns are filtered through a sieve of 710 microns and then a sieve of 300 microns. Particles of 700 to 900 microns are filtered through a sieve of 1000 microns and then a sieve of 500 microns. Particles of 900 to 1200 microns are filtered through a sieve of 1180 microns and then a sieve of 710 microns.

The filtered particles are sterilized by a low temperature technique such as e-beam irradiation, and packaged, typically about 1 to 5 ml of particles in about 5 to 10 ml saline. In embodiments, electron beam irradiation can be used to pharmaceutically sterilize the particles to reduce bioburden. In e-beam sterilization, an electron beam is accelerated using magnetic and electric fields, and focused into a beam of energy. This resultant beam can be scanned by means of an electromagnet to produce a "curtain" of accelerated electrons. The accelerated electron beam penetrates the collection of embolic particles to confer upon them electrons which destroy bacteria and mold to sterilize and reduce the bioburden in the embolic particles. Electron beam sterilization can be carried out by sterilization vendors such as Titan Scan, Lima, Ohio.

Examples

Example 1

Embolic particles are manufactured from an aqueous solution containing 8 weight % of polyvinyl alcohol, 99+% hydrolyzed, average M_w 89,000-120,000 (ALDRICH) and 2 weight% of gelling precursor, sodium alginate, PRONOVA UPLVG, (FMC BioPolymer, Princeton, NJ) in deionized water and the mixture is heated to about 121° C. The solution has a viscosity of about 310 centipoise at room temperature and a viscosity of about 160 cps at 65°C. Using a syringe pump (Harvard Apparatus), the mixture is fed to drop generator (Nisco Engineering). Drops are directed into a gelling vessel containing 2 weight % of calcium chloride in deionized water and stirred with a stirring bar. The calcium chloride solution is decanted within about three minutes to avoid substantial leaching of the polyvinyl alcohol from the drops into the solution. The drops are added to the reaction vessel containing a solution of 4% by weight of formaldehyde (37 wt% in methanol) and 20% by weight sulfuric acid (95-98% concentrated). The reaction solution is stirred at 65°C for 20 minutes. Precursor particles are rinsed with deionized water (3 X 300 mL) to remove residual acidic solution. The sodium alginate is substantially removed by soaking the precursor particles in a solution of 5 weight % of sodium hexa-methaphosphate in deionized water for 0.5 hour. The solution is rinsed in deionized water to remove residual phosphate and alginate. The particles are filtered by sieving, as discussed above, placed in saline (USP 0.9% NaCl) and followed by irradiation sterilization.

Particles were produced at the nozzle diameters, nozzle frequencies and flow rates (amplitude about 80% of maximum) described in Table I.

TABLE 1

Bead Size (microns)	Nozzle Diameter (microns)	Frequency (kHz)	Flow Rate (mL/min)	Density (g/mL)	Sphericity	Suspendability (minutes)
500-700	150	0.45	4	-	0.92	3
700-900	200	0.21	5	1.265	0.94	5
900-1200	300	0.22	10	-	0.95	6

Suspendability is measured at room temperature by mixing a solution of 2 ml of particles in 5 ml saline with contrast solution (Omnipaque 300, Nycomed,

Buckinghamshire, UK) and observing the time for about 50% of the particles to enter suspension, i.e. have not sunk to the bottom or floated to the top of a container (about 10 ml, 25 mm dia vial). Suspendability provides a practical measure of how long the particles will remain suspended in use. (Omnipaque is an aqueous solution of Iohexol, N.N.-Bis (2,3-dihydroxypropyl)-T-[N-(2,3-dihydroxypropyl)-acetamide]-2,4,6-trilodo-isophthalamide; Omnipaque 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per ml. The specific gravity of 1.349 of 37° C and an absolute viscosity 11.8 cp at 20° C.) The particles remain in suspension for about 2 to 3 minutes.

Particle size uniformity and sphericity is measured using a Beckman Coulter RapidVUE Image Analyzer version 2.06 (Beckman Coulter, Miami, FL). Briefly, the RapidVUE takes an image of continuous-tone (gray-scale) form and converts it to a digital form through the process of sampling and quantization. The system software identifies and measures particles in an image in the form of a fiber, rod or sphere. Sphericity computation and other statistical definitions are in Appendix A, attached, which is a page from the RapidVUE operating manual.

Referring to **FIG. 5**, particle size uniformity is illustrated for particles 700 – 900 micron. The x-axis is the particle diameter. The y-axis is the volume normalized percentage of particles at each particle size. The total volume of particles detected is computed and the volume of the particles at each diameter is divided by the total volume. The embolic particles have distribution of particle sizes with variance of less than about $\pm$ 15%.

Example 2

Referring to **FIG. 6**, a catheter compression test investigates the injectability, and indirectly, the compressibility of the particles. The test apparatus includes a reservoir syringe **610** and an injection syringe **620** coupled to a T-valve **630**. Syringe **610** is a 20mL syringe while injection syringe **620** is a 3 mL syringe. T-valve **630** is coupled in series to a second T-valve **640**. T-valve **640** is coupled to a catheter **650** and a pressure transducer **660**. Injection syringe **620** is coupled to a syringe pump **621** (Harvard Apparatus).

To test deliverability of the particles, syringe **610** and syringe **620** are loaded with embolic composition in saline and contrast (50/50 Ominipaque 300). The embolic composition in syringes **610** and **620** is intermixed by turning the T-valve to allow fluid between the syringes to mix and suspend the particles. After mixing, the embolic

composition in syringe **620** flows at a rate of about 10mL/min. The back pressure generated in the catheter **650** is measured by the pressure transducer **670** in millivolts to measure the clogging of catheter **650**. About 1 ml of the particles is mixed in 10mL of solution.

Results for several different catheters (available from Boston Scientific, Natick, MA) and particle sizes are shown in Table 2. The baseline pressure is the pressure observed when injecting carrier fluid only. The delivery pressure is the pressure observed while delivering particles in carrier fluid. The average is the average of the peak pressure observed in the three runs.

SIZE (microns)	Delivery Catheter	Inner Diameter (inches)	Avg. Baseline Pressure (psia)	Avg. Delivery Pressure (psia)	Total number of Clogs
500-700	RENEGADE ®	0.021 (533 micron)	32.610	33.245	0
700-900	FASTRACKER®	0.024 (609 micron)	11.869	13.735	0
900-1200	GLIDECATH ®	0.038 (965 micron)	0.788	0.864	0

As evident, particles in each of the size ranges were successfully delivered without clogging through catheters having a lumen diameter smaller than the largest particle size. The particles exhibit a post-compression sphericity of about 0.9 or more.

Example 4

Solubility is tested by mixing particles in a solution of solvent at room temperature for about 0.5 hour and observing the mixture for visible signs of dissolution. The particles are insoluble in DMSO (Dimethylsulfoxide), HFIP (Hexafluoro-isopropanol), and THF (Tetrahydrafuran).

Example 5

Embolic particles include the following glass transition temperatures as measured by differential scanning calorimetry data (DSC)

Product	500-700 microns	900-1200 microns
Glass transition temperature (Tg)	109.30-110.14	108.30-111.87

Example 6

Referring to Fig. 7, an ATR infrared spectrum of dried particles is provided.

Use

The embolic compositions can be used as pharmaceutically acceptable compositions in the treatment of, for example, fibroids, tumors, internal bleeding, AVMs, hypervascular tumors, fillers for aneurysm sacs, endoleak sealants, arterial sealants, puncture sealants and occlusion of other lumens such as fallopian tubes. Fibroids can include uterine fibroids which grow within the uterine wall (intramural type), on the outside of the uterus (subserosal type), inside the uterine cavity (submucosal type), between the layers of broad ligament supporting the uterus (interligamentous type), attached to another organ (parasitic type), or on a mushroom-like stalk (pedunculated type). Internal bleeding includes gastrointestinal, urinary, renal and varicose bleeding. AVMs are for example, abnormal collections of blood vessels, e.g. in the brain, which shunt blood from a high pressure artery to a low pressure vein, resulting in hypoxia and malnutrition of those regions from which the blood is diverted.

The magnitude of a therapeutic dose of the embolic composition can vary based on the nature, location and severity of the condition to be treated and the route of administration. A physician treating the condition, disease or disorder can determine effective amount of embolic composition. An effective amount of embolic composition refers to the amount sufficient to result in amelioration of symptoms or a prolongation of survival of the patient. The embolic compositions can be administered as pharmaceutically acceptable compositions to a patient in any therapeutically acceptable

dosage, including those administered to a patient intravenously, subcutaneously, percutaneously, intratrachealy, intramuscularly, intramucosaly, intracutaneously, intra-articularly, orally or parenterally.

Compositions containing the embolic particles can be prepared in calibrated concentrations of the embolic particles for ease of delivery by the physician. The density of the composition can be from about 1.1 to 1.4 g/cm^3, or from about 1.2 to about 1.3 g/cm^3 in saline solution. Suspensions of the embolic particles in saline solution can be prepared to form stable suspensions over duration of time. The suspensions of embolic particles can be stable from 1 to 10 minutes, 2-7 minutes or 3 to 6 minutes. The physician can determine concentration of embolic particles by adjusting the weight ratio of the embolic particles to physiological solution. If weight ratio of the embolic particles is too small, too much liquid could be injected in a blood vessel, possibly allowing the embolic particles to stray into lateral vessels. In embodiments, the weight ratio of the embolic particles to the physiological solution is about 0.01 to 15% by weight. The embolic composition can include a mixture of particles including particles with the pore profiles discussed above and particles with other pore profiles or non-porous particles. Particles can be used for embolic applications without removal of the gelling agent (e.g. alginate) for example at the stabilized drop stage or precursor particle stages described above. While substantially spherical particles are preferred, non-spherical particles can be manufactured and formed by controlling, e.g. drop formation conditions or by post-processing the particles, e.g. by cutting or dicing into other shapes. Particles can also be shaped by physical deformation followed by crosslinking. Particle shaping is described in U.S. Serial No. 10/116,330 filed April 4, 2002, the entire contents of which is hereby incorporated by reference.

Other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. An embolic composition, comprising:

substantially spherical embolic particles having a diameter of about 1200 micron or less, the particles comprising polyvinyl alcohol, and including an interior having relatively large pores and a surface region having fewer relatively large pores.

2. The composition of claim 1 wherein the relatively large pores are about 20 micron or more.

3. The composition of claim 1 wherein the relatively large pores are about 30 micron or more.

4. The composition of claim 1 wherein the surface region is about r to 0.8r.

5. The composition of claim 1 wherein the surface region is about r to 2/3r.

6. The composition of claim 4 including a body region from about 2/3r to $^{r}/_{3}$ including intermediate size pores and the body region has more intermediate size pores than the surface region.

7. The composition of claim 6 including a center region from about $^{r}/_{3}$ to C, the outer region including large size pores and the body region has fewer large size pores than the center region.

8. The composition of claim 7 wherein the large size pores are about 20 micron or more.

9. The composition of claim 8 wherein the intermediate size pores are about 2 to 18 microns.

10. The composition of claim 1 wherein the surface region is substantially free of pores greater than about 5 micron.

11. The composition of claim 1 wherein the predominant pore size generally, progressively increases from surface to the center of the particle.

12. The composition of claim 1 wherein the predominant pore size on the particle surface is about 1 micron or less.

13. The composition of claim 1 wherein the particles have a surface region from about $^{(2r)}/_{3}$ to the surface wherein the predominant pore size is in the range of about 1 micron or less.

14. The composition of claim 13 wherein the predominant pore size is about 0.1 micron or less.

15. The composition of claim 13 wherein the particles, interior of said surface region, have a predominant pore size in the range of about 2 to 35 microns.

16. The composition of claim 14 wherein the particles include a region from about r to $^{r}/_{3}$ in which the predominant pore size is about 20 to 35 micron.

17. The composition of claim 15 wherein the particles have a body region from $^{r}/_{3}$ to $^{(2r)}/_{3}$ in which the predominant pore size is about 2 to 18 micron.

18. The composition of claim 1 wherein the particles have a surface region from about $^{(2r)}/_{3}$ to the surface and the predominant pore size in the surface region is about 10% or less than the predominant pore size in the interior to the surface region.

19. The composition of claim 1 wherein the particles have a density of about 1.1 to about 1.4 g/cm^3.

20. The composition of claim 1 wherein the particles have a density of about 1.2 to 1.3 g/cm^3.

21. The composition of claim 1 wherein the embolic particles have a sphericity of about 90% or more.

22. The composition of claim 21 wherein the particles have an initial sphericity of about 97% or more.

23. The composition of claim 22 wherein the particles have a sphericity of about 0.90 after compression to about 50%.

24. The composition of claim 1 wherein the collection has a size uniformity of about $\pm$ 15% or more.

25. The composition of claim 1 wherein the particles include about 1% or less polysaccharide.

26. The composition of claim 25 wherein the polysaccharide is alginate.

27. The composition of claim 26 wherein the alginate has a guluronic acid content of about 60% or greater.

28. The composition of claim 1 wherein the embolic particles are substantially insoluble in DMSO.

29. The composition of claim 1 wherein the embolic particles are substantially free of animal-derived compounds.

30. The composition of claim 1 wherein the polyvinyl alcohol is composed of substantially unmodified polyvinyl alcohol prepolymer.

31. The composition of claim 1 wherein the polyvinyl alcohol is predominantly intrachain 1, 3-diols acetalized.

32. The composition of claim 1 wherein the collection is in a pharmaceutically acceptable medium.

33. The composition of claim 32 wherein the medium comprises saline.

34. A method of manufacturing embolic particles comprising:
generating drops comprising a base polymer and a gelling compound;
reacting the base polymer;
removing the gelling compound; and
combining the particles with a pharmaceutically acceptable medium.

35. The method of claim 34 wherein the gelling compound is a polysaccharide.

36. The method of claim 35 wherein the gelling compound is alginate.

37. The method of claim 36 wherein the alginate has a guluronic acid content of about 60% or more.

38. The method of any one of claims 34-37 comprising contacting the drops with a gelling agent.

39. The method of claim 38 wherein the gelling agent is a divalent cation.

40. The method of claim 39 wherein the cation is Ca^{+2}.

41. The method of claim 1 wherein base polymer is PVA.

42. The method of claim 41 comprising reacting the PVA by acetalization.

43. The method of claim 41 or 42 wherein the PVA has a molecular weight of about 75,000 g/mole or greater.

44. The method of claim 1 comprising modifying the viscosity of the base polymer and gelling compound in forming said drops.

45. The method of claim 44 comprising modifying the viscosity by heating.

46. The method of claim 1 comprising forming said drops by vibratory nebulization.

47. A method comprising administering to a patient in need of embolization a therapeutically effective amount of substantially spherical embolic polymer particles, the particles comprising polyvinyl alcohol, and including an interior region having relatively large pores and a surface region having fewer relatively large pores.

48. The method of claim 47 wherein the method of administration is by percutaneous injection.

49. The method of claim 47 wherein the method of administration is by a catheter.

50. The method of claim 47 wherein the particles are introduced to the body through a lumen, and the lumen of a medical device has a smaller diameter than the particles.

51. The method of claim 47 for treatment of uterine fibroids.

52. The method of claim 47 for treatment of a tumor.

53. The method of claim 47 for treatment of arteriovenous tumors.

54. An embolic composition, comprising:

embolic polymer particles having a diameter of about 1200 micron or less, and including a surface with a predominant pore size of about 2 micron or less and pores interior to said surface of about 10 micron or more.

55. The composition of claim 54 wherein the particles include a surface region from about 0.8r to r wherein the predominate pore size is about 1 micron or less.

56. The composition of claim 55 wherein particles include a region from about C to 0.8r includes pores having a diameter of 10 microns or more.

57. The composition of claim 56 wherein the region C to 0.8r has a predominant pore size of about 3.5 to 2 micron.

58. An embolic composition comprising:

embolic polymer particles including a surface region from about 0.8r to r, the predominant pore size in the surface region being smaller than the predominant pore size in a region C to 0.3r.

59. An embolic composition, comprising:

embolic particles including a surface region defined primarily by small pores and an interior region defined primarily by relatively large pores.

60. The composition of claim 58 or 59 wherein the embolic particles are substantially spherical.

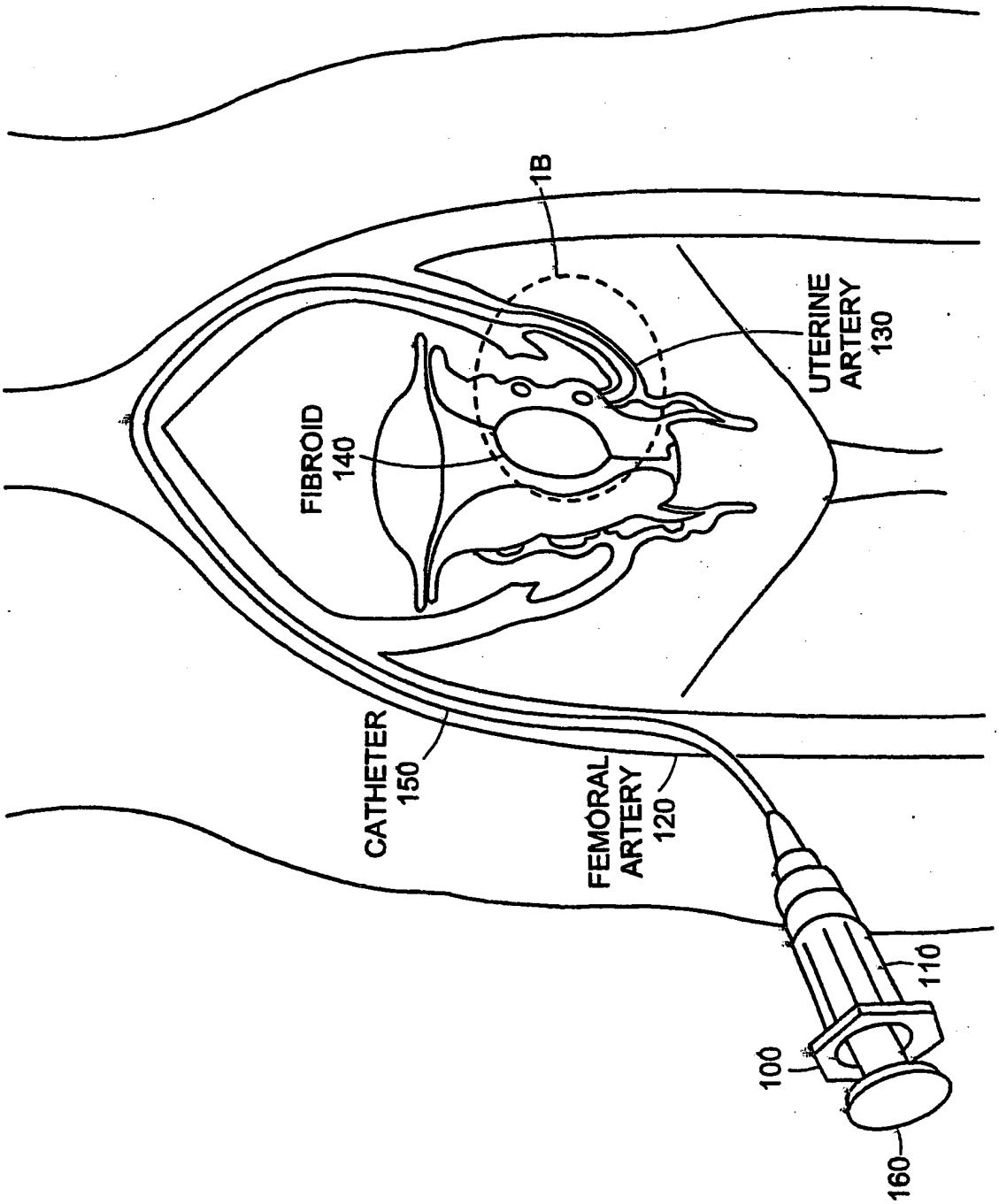

1B
UTERINE ARTERY 130
FIBROID 140
CATHETER 150
FEMORAL ARTERY 120
110
100
160

FIG. 1A

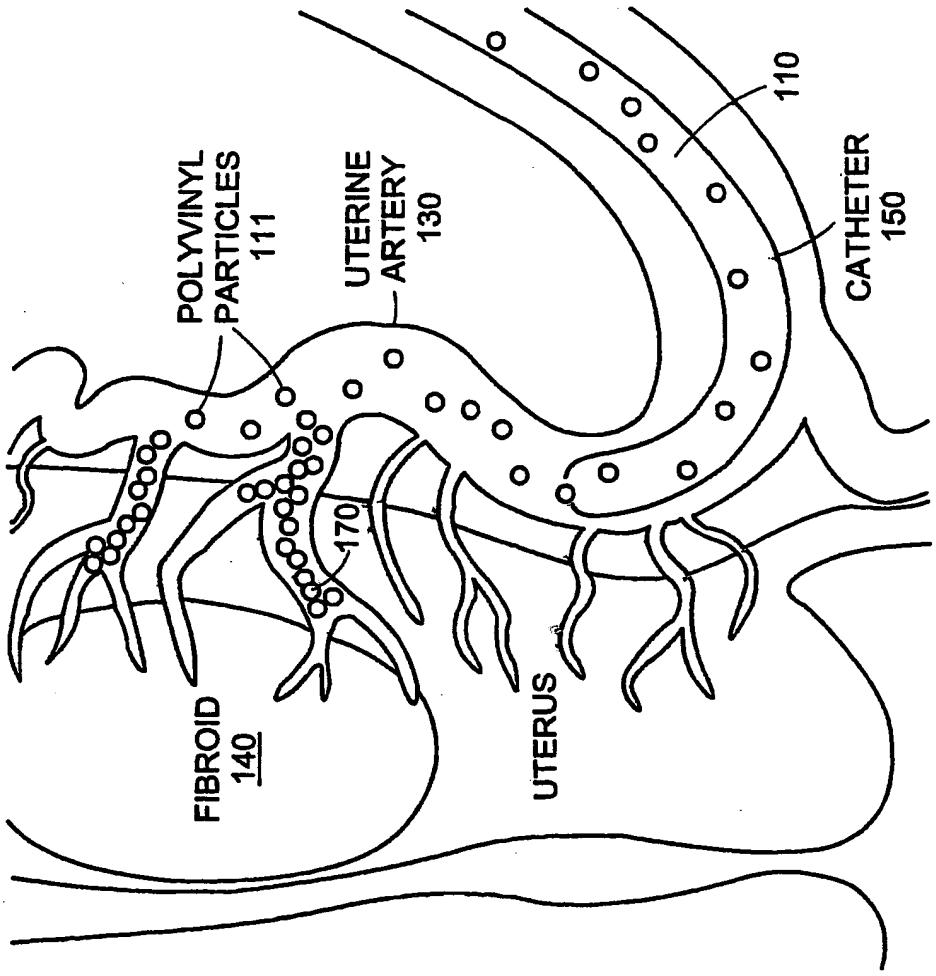

POLYVINYL PARTICLES 111
UTERINE ARTERY 130
110
CATHETER 150
170
FIBROID 140
UTERUS

FIG. 1B

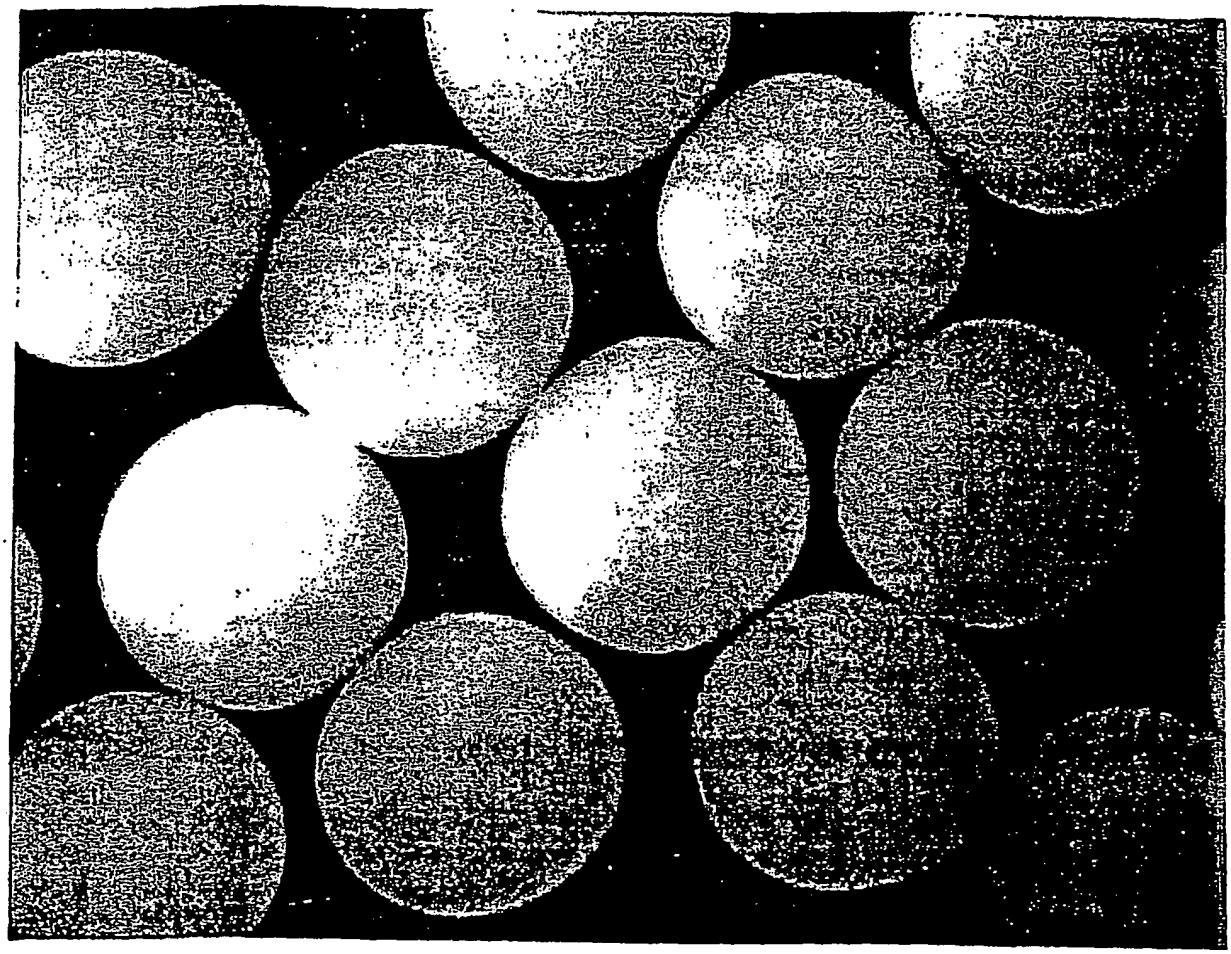


FIG. 2A

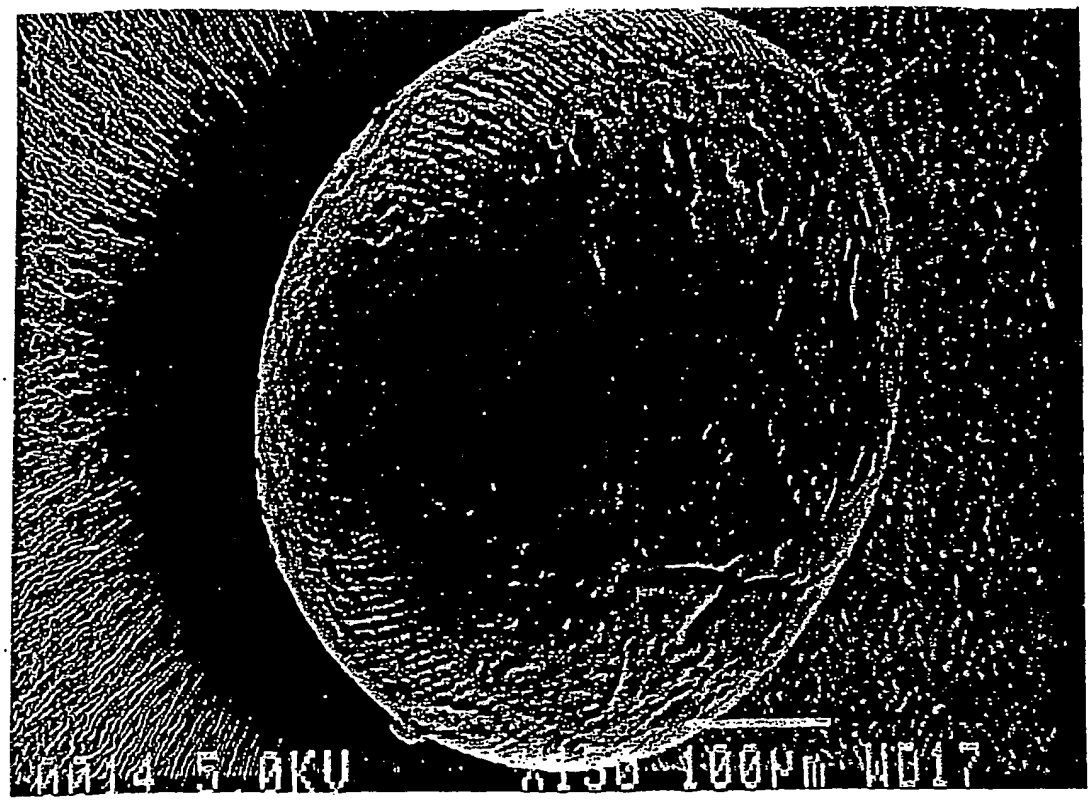


FIG. 2B

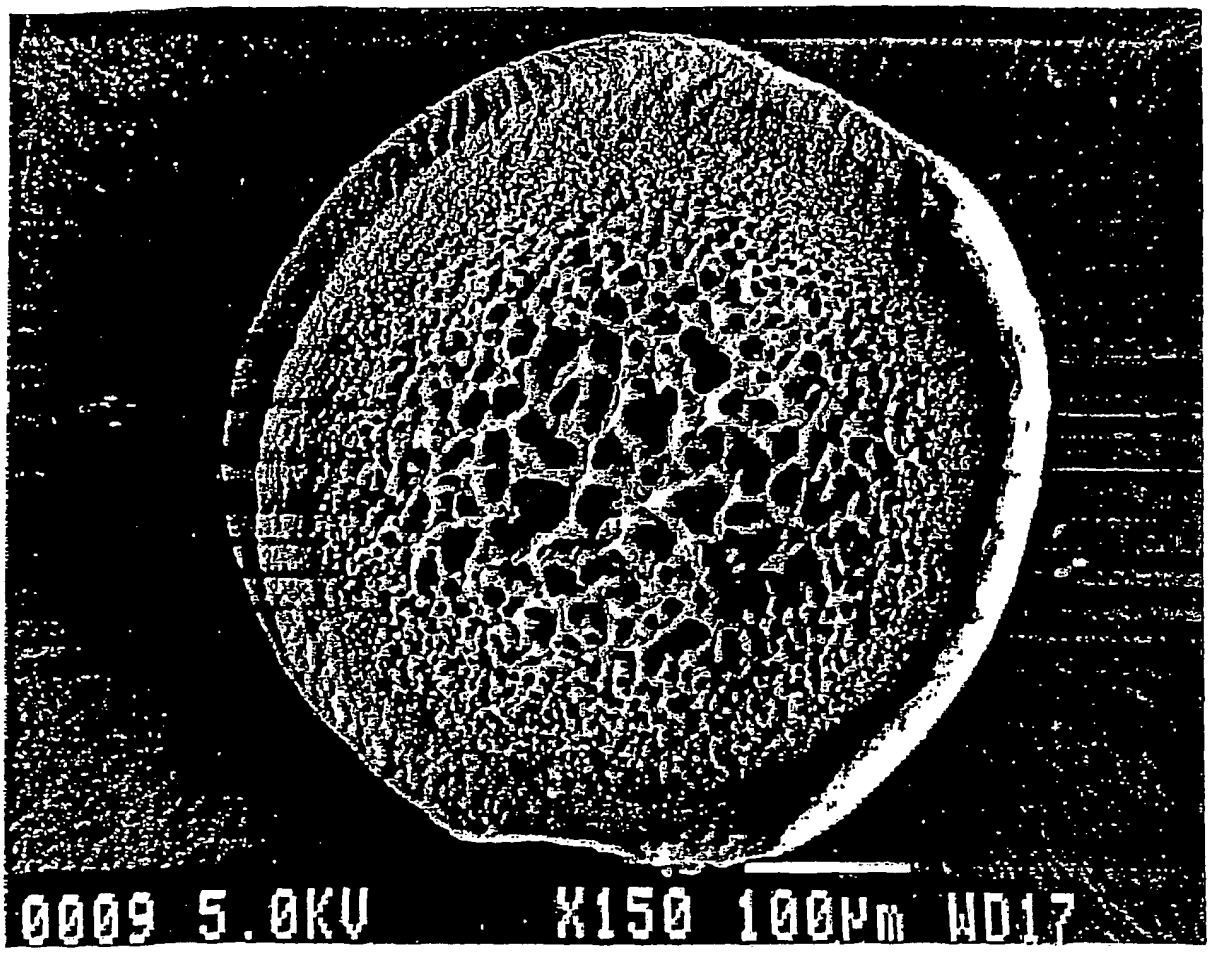
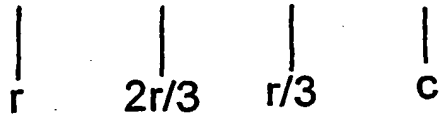


FIG. 2C



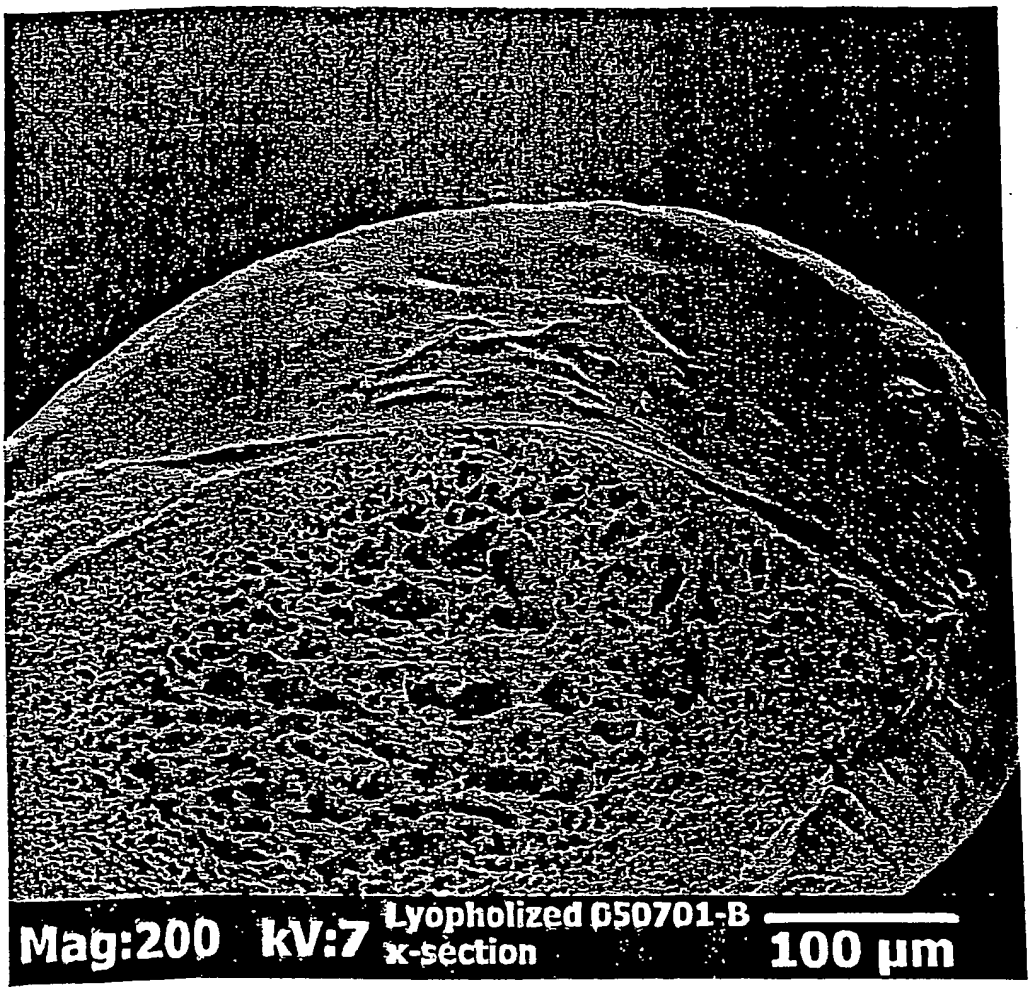


FIG 2D

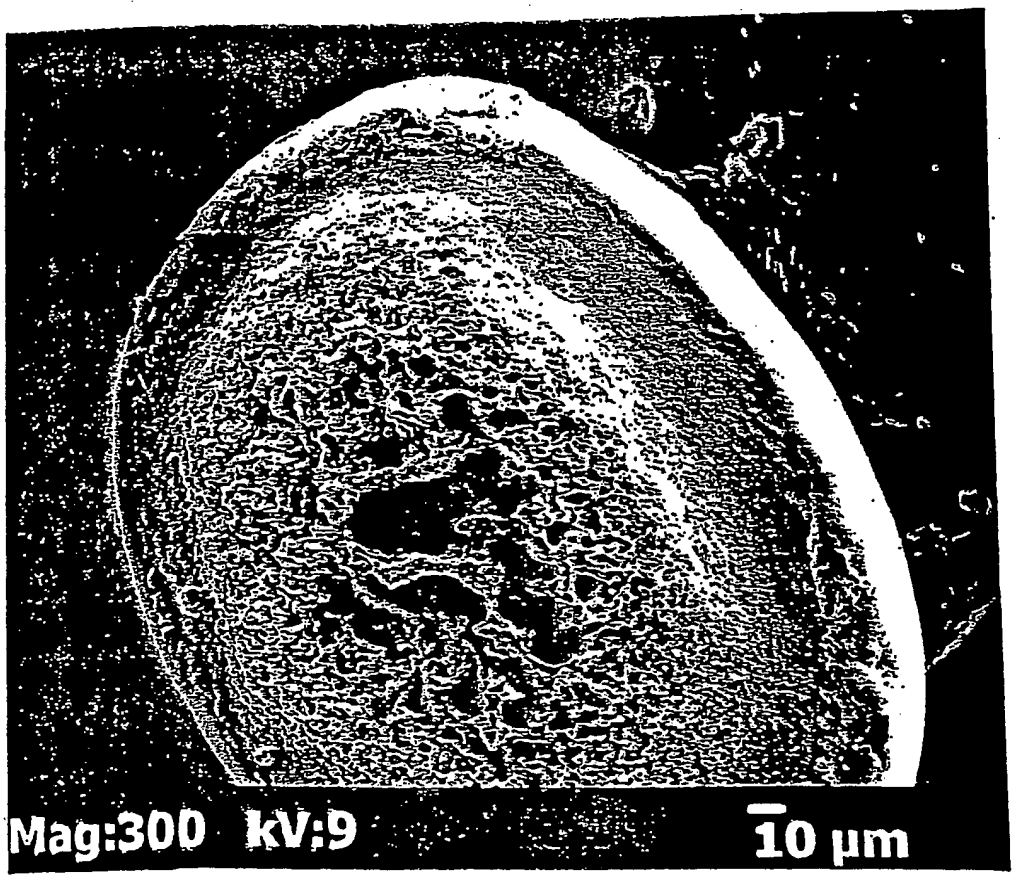


FIG. 2E

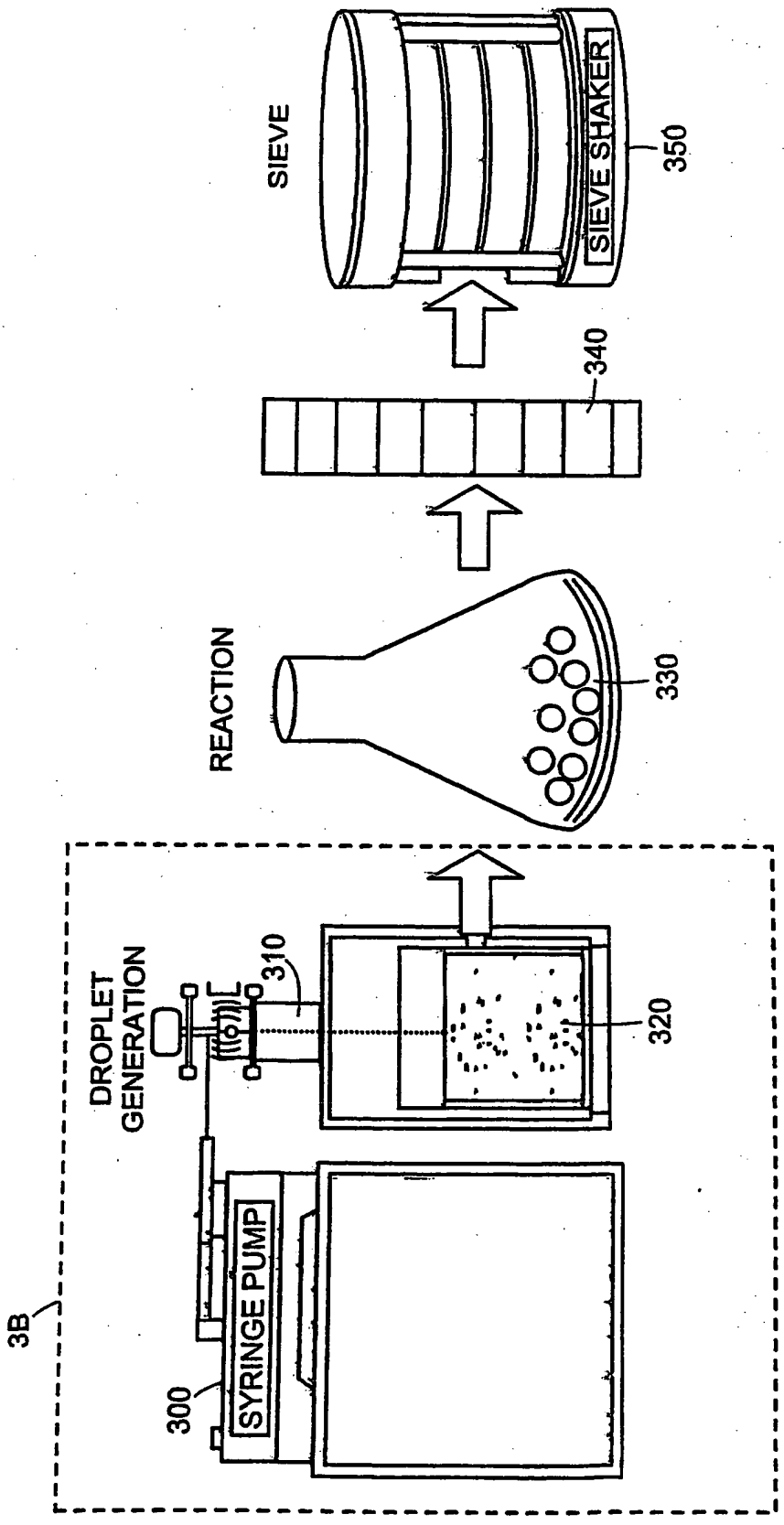

SIEVE
SIEVE SHAKER
350
340
REACTION
330
DROPLET GENERATION
310
320
3B
300
SYRINGE PUMP

FIG. 3A

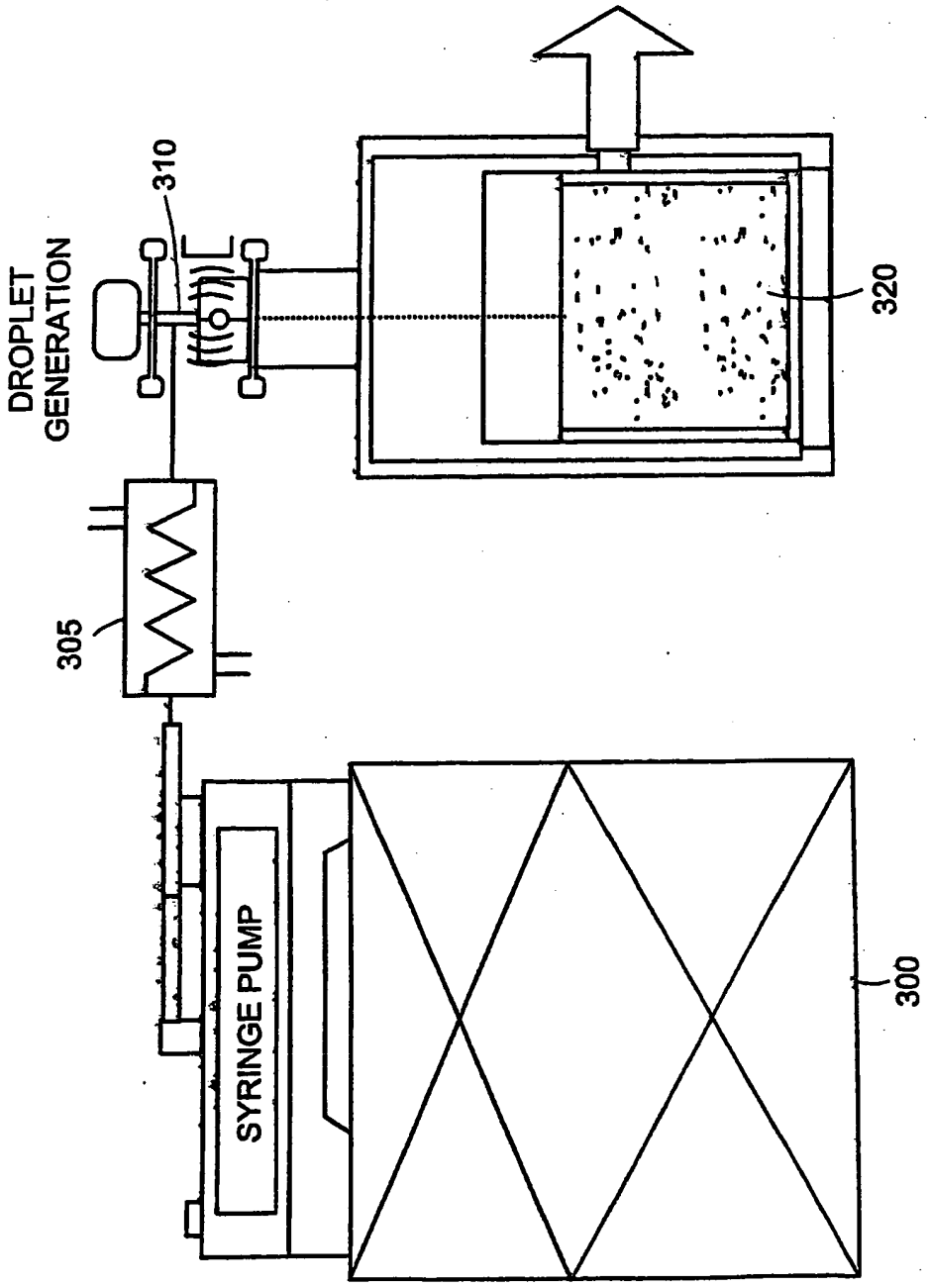


FIG. 3B

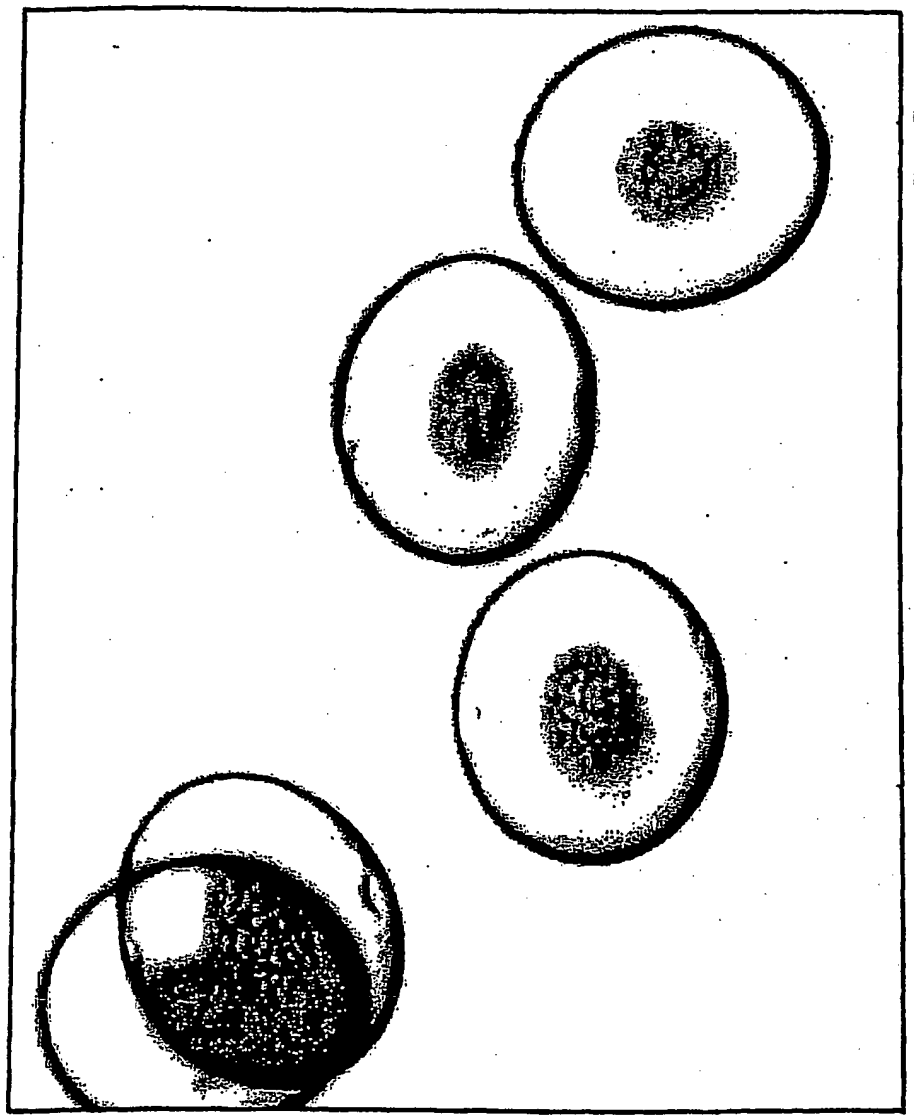


FIG. 4

ECA DIAMETER DIFFERENTIAL VOLUME
600.0 - 1400.0 MICRONS

TOTAL COUNT	958
MEAN	810.7 MICRONS
STANDARD DEVIATION	102.4 MICRONS
COEFFICIENT OF VARIANCE	12.63%
HARMONIC MEAN	800.4 MICRONS
MODE	783.6 MICRONS
SKEWNESS	2.26
10%	730.2 MICRONS
25%	755.2 MICRONS
50%	785.8 MICRONS
75%	816.4 MICRONS
90%	954.1 MICRONS
PERCENT OF TOTAL	100.00%

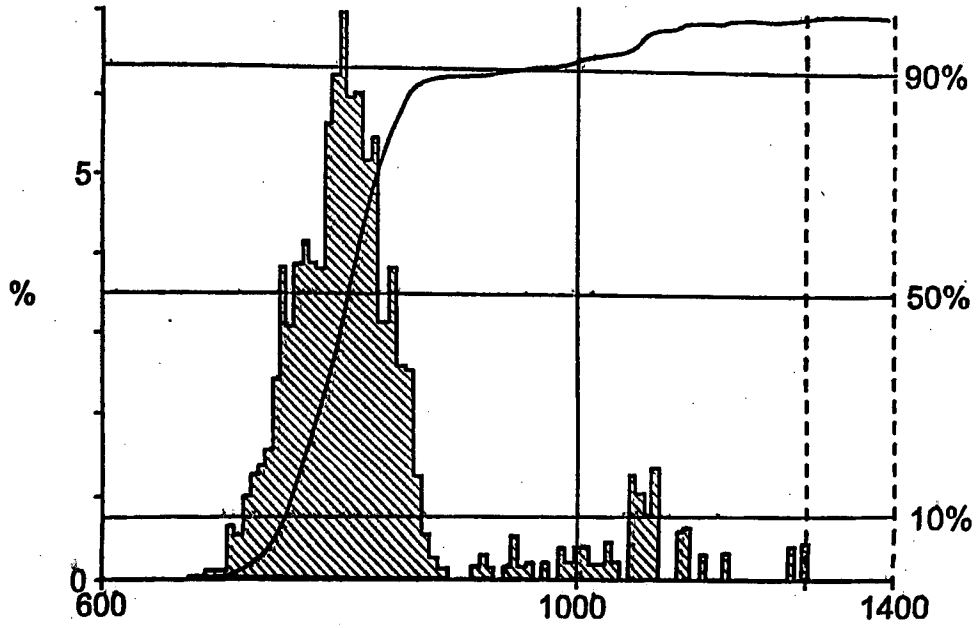


FIG. 5

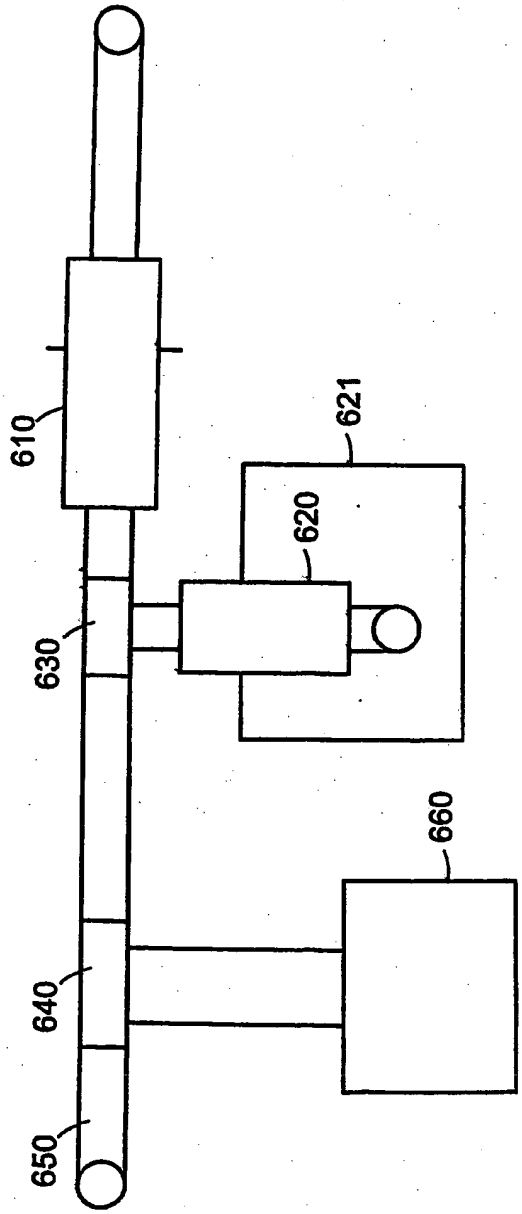


FIG. 6

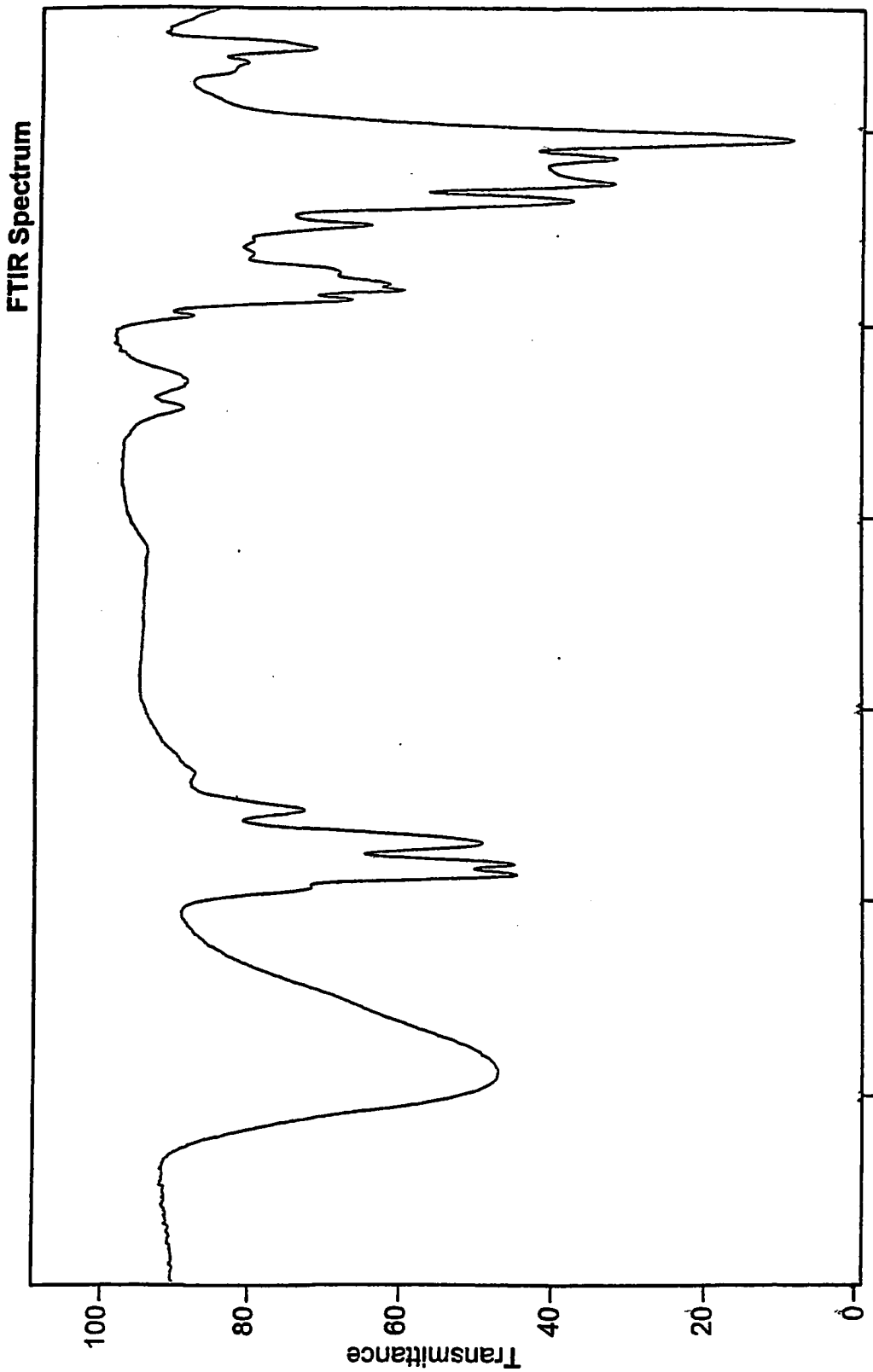

FTIR Spectrum
Transmittance
100
80
60
40
20
0
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
Res = 4cm-1

FIG. 7

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L24/04 A61L24/00 A61L27/50 A61L27/16 A61L31/04
A61L31/14 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/051670 A1 (ASFAW BRUKTAWIT T ET AL) 13 December 2001 (2001-12-13) page 8; claims	1-60
Y	DE 100 26 620 A (QUELLE GERHARD) 7 March 2002 (2002-03-07) claims	1-60
Y	EP 0 730 847 A (MENLO CARE INC) 11 September 1996 (1996-09-11) claims	1-60
A	WO 01 70291 A (BIOSPHERE MEDICAL INC) 27 September 2001 (2001-09-27) claims	1-60

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2003	19/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ESPINOSA, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 19702 A (UROPLASTY INC) 14 October 1993 (1993-10-14) claims	1-60
A	EP 0 402 031 A (AMERICAN MED SYST) 12 December 1990 (1990-12-12) claims	1-60
A	DE 94 14 868 U (GUENTHER ROLF W PROF DR MED ;KLEIN HANS MARTIN (DE)) 15 December 1994 (1994-12-15) claims	1-60
A	US 6 224 630 B1 (YUAN HANSEN A ET AL) 1 May 2001 (2001-05-01) claims	1-60

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/09408

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 47-53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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